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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,306	12/08/2000	Margaret A. Schwarz	9022.20	3192

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,306	SCHWARZ, MARGARET A.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The sequence listing submitted 1-09-03 is technically sound and has been entered into the sequence database of the STIC division of the USPTO.

Response to Arguments

Claim Rejections - 35 USC § 112

3. Claims 1-2, 4-12 and 14-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the claimed method by the administration of monoclonal antibodies targeting EMAP II, does not reasonably provide enablement for practicing the claimed method comprising the administration of antisense oligonucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth in the Official Action mailed 11-06-01.

4. Applicant's arguments filed 8-12-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection of the grounds that since Applicants have demonstrated improved myocardial function by administration an anti-EMAP II monoclonal antibody in an animal model of myocardial infarction, that one skilled in the art would be able to carry out other methods of inhibiting EMAP II activity to achieve the claimed effects without undue experimentation. Moreover, Applicants argue that in view of Applicant's demonstration that inhibition of EMAP II protein post-infarction in an animal model can improve myocardial infarction (Example 1), one skilled in the art would be able to routinely identify an antisense

oligonucleotide to the EMAP II sequence having similar effects. Furthermore, Applicant's argue that based upon Galderisi et al. (1999) and Orr (2001), antisense technology has been successfully employed in the treatment of a disease state. In regards to the legal standard for establishing a prima facie case for lack of an enabling disclosure, the Office Action mailed 11-06-2001 clearly set forth the appropriate legal standard as per MPEP § 2164.01(a). MPEP § 2164.01(a) describes the factors for determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

First, it is noted that in regards to the breadth of the claimed invention, the instant claims do not recite any particular nucleotide structure corresponding to EMAP II, such that the structure of the antisense oligonucleotides used in the claimed method would be immediately envisioned. Therefore, the claims encompass targeting all allelic, and polymorphic variants of EMAP II isolated from any species of subject, and furthermore the claimed methods read on the administration of any type of subject.

Secondly, in regards to the amount of direction provided in the specification as filed, Applicants have not reduced to practice the claimed method as it relates to the administration of an antisense oligonucleotide, Applicants do not disclose the structure of any antisense oligonucleotide that is capable of inhibiting expression of EMAP II. Moreover, applicants do not

provide any evidence that the methods for administration of antibodies targeting EMAP II in Example I would be effective to administer antisense compounds, and furthermore would be useful for successfully delivering an amount of antisense compound effective to stimulate vascular growth in cardiac muscle. Antisense oligonucleotides and antibodies are chemically and structurally distinct molecules, are metabolized by distinct compounds, function in distinct manners and have separate modes of action and activity. One of skill in the art would not accept on its face, that the activity of a structurally distinct compound could be used to predict the behavior of another chemically and structurally distinct compound.

Thirdly, in regards to the level of unpredictability in the art associated with antisense therapeutic treatment of diseases, as stated in the prior Office Action, there is a high level of unpredictability in the art for any method of treatment with a therapeutic agent for treating a disease or causing a particular physiological condition when the cite of action of the pharmaceutical composition is not clear, when the target site is not readily accessible or the compound does not readily find the target of action, and when the action of the pharmaceutical composition on other parts of the whole organism are unknown.

For instance, in the antisense art is unpredictable to design any antisense to a target gene for use in therapeutic situations since the factors considered barriers to successful delivery of antisense delivery to an are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense

molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunately, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of any antisense molecule to EMAPII *in vivo* and further, treatment effects, in view of the breadth of the claimed invention, lack of guidance in the specification and the unpredictability in the art. Neither the specification nor the technology today provides general guidelines for successful delivery and/or treatment effects of antisense molecules in general, in whole organisms.

Although, there may be several very specific examples of using antisense oligonucleotides *in vivo,* as per Applicant's reference to Galdersi et al. (1999) and Orr (2001), however there is no reference to a commonly known method for administration of antisense oligonucleotides, wherein administration of any antisense oligonucleotide *in vivo,* specifically produces reduction in gene expression with the concomitant therapeutic result directly associated with the reduction in gene expression. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed for design of antisense and delivery to whole organisms for the claimed functions.

5. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods comprising inhibiting EMAP II activity. However, the claims do not recite any particular nucleotide sequence and/or amino acid sequence to describe the structure of EMAP II. Since there is no structure recited in the instant claims to describe the EMAP II of the claimed invention, the instant claims read on EMAP II isolated for

any organism, including all polymorphic and allelic variants, as well as any splice variants that my encode EMAP II. However, the specification as filed provides only a brief reference to human EMAP II according to GenBank Accession No. 10119. It is noted that the instant claims are not limited to human EMAP II, or furthermore human EMAP II according to GenBank Accession No. 10119. Moreover, Applicant's reference to human EMAP II does not provide sufficient description such that the skilled artisan could envision all forms of EMAP II encompassed by the instant claims. Moreover, since applicants have not described all forms of EMAP II encompassed by the instant claims, it is impossible for the skilled artisan to envision the full scope of antisense and/or antibodies that would be useful to practice the claimed invention as well.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Since Applicants have not provided a clear and precise description of the full scope of compounds encompassed by the instant claims. Applicant's were not in possession of the full scope of the claimed methods recited in the instant claims.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 09/928,796. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of facilitating vascular growth in cardiac muscle of a subject comprising inhibiting EMAP II activity in a subject by an amount effective to stimulate vascular growth as recited in the instant claims are fully encompassed by the generic method for facilitating vascular growth in a subject comprising inhibiting EMAP II activity as recited in claims 1-4 of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE